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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Group Art Unit: 1615
SOPHIE GAUBERT et al Examiner: G. Kishore
Serial No.: 10/069,050 MAIL STOP AFTER FINAL

Filed: March 7, 2002

For: COMPOSITION TO BE ADMINISTERED THROUGH MUCOUS MEMBRANE

RESPONSE

Honorable Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

The following remarks are submitted in response to the Office Action mailed February 8, 2005.

Claims 16-19, 21-33 and 35-65 stand rejected under 35 USC 103(a) over Haan et al by itself, or in combination with Doerschuk and Roux, or over Wassef et al in combination with Haan et al by itself, or in combination with Doerschuk and Roux.

Upon careful analysis, it can be determined that the teachings of Haan et al are actually contrary to the claimed invention.

The teaching of Haan et al is that there are two mechanisms for the induction of immune response after mucosal immunization.

A first mechanism is at the origin of the response obtained by El Guink, cited by Haan et al. Haan et al explains that in the case of the El Guink experiments, a very specific system had been used, where "the viral surface

glycoprotein has been reconstituted in the liposomal membrane to form a proteoliposome" (cf. page 160, column 2, 2nd §).

The second mechanism is the one described by Haan et al in the cited article, and is completely different. The Haan et al hypothesis is based on the fact that alveolar macrophages are known to suppress immune response in the lung, since they capture and destroy any particle before it reaches the mucous membrane. This is the so-called "macrophage-mediated immune suppression" (cf. page 161, column 1, 1st §). Haan et al suggests that the results obtained could come from the fact that administering high doses of lipids before - or at the time of - immunization could inhibit this immune suppression because of the saturation of the uptake capacity of the macrophages. This would explain why the obtained immune response is the same when the empty liposomes are administered two days before the immunization. Haan et al explains that the lipids of the liposomes are used to saturate the macrophages, as it is important to avoid having the antigen captured by the alveolar macrophages. Thus, in order for this mechanism to work, **it is important that the antigen be liberated from the liposome before the liposome is captured by the macrophages. It is therefore important to have liposomes not too resistant to degradation.**

It follows logically that the teaching of this article is that in order to obtain a high immune response following mucosal immunization, one should either make a proteoliposome, or to use liposomes which liberate their antigen before reaching the alveolar macrophages, i.e. to have *fragile* liposomes.

The vesicles used according to the present application are not proteoliposomes. Furthermore, due to their liquid-crystal structure, the vesicles according to the present

application are known to be particularly *stable* and much *more stable* than conventional liposomes. Following the teaching of Haan et al, it could be expected that these multilamellar vesicles would be captured by the alveolar macrophages before they have liberated their antigen, therefore destroying the antigen and preventing it from reaching the immune system.

One of ordinary skill in the art would therefore have expected to obtain weaker response using the vesicles of the invention than using classical liposomes, and would not have been induced to use the vesicles of the invention for mucosal administration of vaccine.

The Final Office Action has noted that Applicants have previously argued that Haan et al requires a negatively charged phospholipid, whereas the claimed invention does not include any limitation at all regarding phospholipids.

Indeed, Haan et al specifies on page 159, col. 2, 1st §, that negative results are obtained with non-negatively charged phospholipids. Therefore, there is nothing in Haan et al which suggests to those skilled in the art that the use of vesicles having the specific structure of the vesicles used according to the present application would enable the use of almost any type of surfactant in the bilayers of the vesicles.

A large variety of surfactants may be used to prepare the vesicles used according to the present application, including neutral phospholipids (see the examples of the present application). The teaching of Haan et al would have suggested to those skilled in the art not to use the phospholipids which Applicants have found to be effective, but only effective when used with presently claimed vesicles.

In the amendment, in answer to the previous Office Action, Applicants proposed that the fact that the vaccine protocol according to Haan et al was not the same as that used

in the examples of the present application shows that the mechanism of action must be different, an argument in favor of the novelty of the present invention. Applicants admit that the present claims do not exclude the Haan et al protocol.

However, due to the use of vesicles having the specific structure claimed, it was possible to obtain excellent results, even with a protocol which was not that which was suggested by Haan et al.

Thus, quite apart from the question of whether only negatively charged surfactants would be effective for liposomes used in vaccination, it has now been shown that Haan et al proposes only two mechanisms for effective vaccination by the nasal route, neither of which is used according to the claimed invention. Indeed, the method of the claimed invention is not related to the used of proteoliposomes, and does not involve the use of an unstable liposome which would release its antibody prior to capture by the macrophages. According to the cited art, the claimed invention would not be expected to be effective, and thus its effectiveness must be deemed to be surprising.

Withdrawal of these rejections is requested.

In view of the foregoing remarks, Applicants submit that the present application is now in condition for allowance. An early allowance of the application claims is earnestly solicited.

Respectfully submitted,



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